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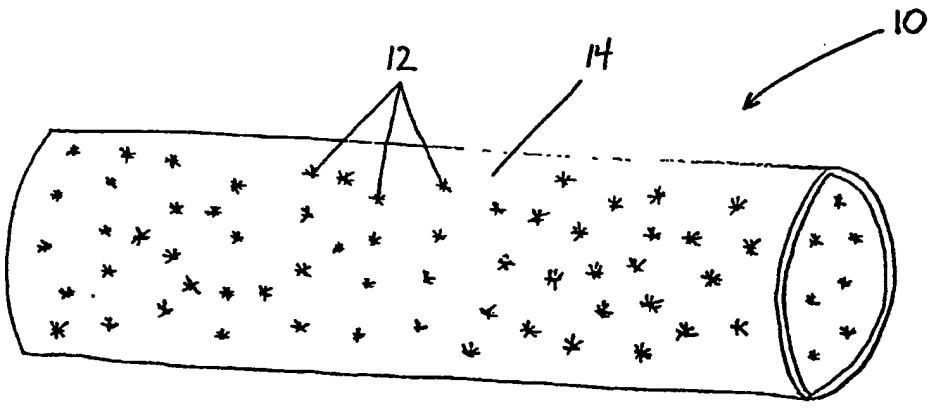
(54) Title: RADIOACTIVE GRAFT OR CUFF



(57) Abstract: Radioactive grafts or cuffs are made by incorporating radioactive elements into a pliable material such as ePTFE. The radioactive grafts or cuffs are placed into the body to prevent the proliferation of malignant cells. For example, a graft or cuff may be used in an occluded lumen after it has been opened to prevent subsequent restenosis. While the grafts are used primarily for implantation inside a body lumen, the cuffs can be used in a variety of locations including being wrapped around the outside of an affected vessel. Some embodiments of the present invention incorporate radioactive seeds into ePTFE grafts. The radioisotopes comprising the seeds are chosen according to their radioactive properties and are mixed with the PTFE prior to extrusion. Following extrusion, the PTFE is expanded and sintered to yield a final product.

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RADIOACTIVE GRAFT OR CUFF

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates generally to the field of medical devices, and more particularly, to devices and methods to avoid vascular restenosis.

2. Description of Related Art

Many devices such as stents have been used by physicians to prevent restenosis of blood vessels following treatments to expand vessels narrowed by arteriosclerosis. Following angioplasty to correct arteriosclerosis restenosis often occurs because such treatments stimulate excess tissue proliferation.

Another solution to the problem of narrowed vessels is to surgically bypass them with a prostheses. Polytetrafluoroethylene (PTFE) has proven advantageous as a material from which to fabricate blood vessel grafts or prostheses. This is partially because PTFE is extremely biocompatible causing little or no immunogenic reaction when placed within the human body. This is also because in its preferred form, *expanded* PTFE (ePTFE), the material is light and porous and can be readily colonized by living cells so that it becomes a permanent part of the body. Unfortunately, the process of suturing such a prosthesis of a living vessel often stimulates cellular proliferation similar to angioplasty. The failure modes of vascular grafts are frequently related to a luminal hyper-proliferative cellular response that eventually affects the flow dynamics resulting in thrombotic events and occlusion of

blood flow. Dialysis access grafts typically fail at the venous anastomotic site due to flow related intimal hyperplasia. Peripherally placed bypass grafts often fail due to intimal thickening at the suture sites.

Clinical research has indicated that ionizing radiation is capable of reducing restenosis and preventing cellular proliferation in vascular applications. However, the concept of Vascular Brachytherapy is relatively new. Although radiation has been used for years in Oncology, its use for the reduction of smooth muscle cell proliferation and the reduction of restenosis in vascular applications is recent. Ionizing radiation has the ability to damage cellular DNA and can either prevent the cells from dividing or can kill them outright. The utilization of a radiation source in vascular graft, especially if incorporated into ePTFE, may have the ability to maintain graft patency for longer periods of time by preventing the hyper-proliferative responses mentioned above.

A major problem with some current methods of treating restenosis through radiation therapy is that the radiation source is present as a fluid within the vascular lumen, such that the possibility of leakage is present, potentially causing major injury to the patient. For example, U.S. Patent No. 5,616,114 to **Thorton et al.** discloses an apparatus and method to deliver radiation to the walls of a blood vessel through the use of a catheter with a balloon tip which balloon can be inflated with radioactive liquid. It would be desirable to provide radioactive therapy to areas of the body without the risk of causing injury to the patient in the event of a leak caused by balloon breakage.

Other methods of using radiation to treat restenosis employ radioactive sources (often metallic) delivered by catheter. A difficulty with this approach is leaving the catheter in the patient's circulatory system for a long enough time to adequately affect restenosis. A radioactive source of adequate strength so as to minimize the indwelling time of the catheter may be so strong as to have a potential for overexposure and prove dangerous to work with. A source weak enough to avoid overexposure danger may result in problems caused by the lengthy indwelling of the delivery catheter. Yet another alternative is to place the radioactive sources on a metal stent. This approach may cause damage through direct contact between the radioactive stent and the vessel. Also, it may be difficult to achieve the desired pattern of radiation because the pattern is determined by the physical construction of the stent.

SUMMARY OF THE INVENTION

The present invention is directed to radioactive grafts or cuffs, wherein radioactive therapy is localized to an afflicted area. This can be accomplished in several different ways by incorporating radioactive elements into vascular grafts or similar implantable medical devices.

It is an object of this invention to provide an implantable medical device that utilizes radiation therapy to prevent excess tissue proliferation especially proliferation resulting in restenosis of blood vessels.

It is also an object of this invention to provide a device for radiation therapy that does not involve the transport of leak-prone radioactive fluid through the body.

These and additional objects are accomplished through the incorporation of radioactive "seeds", coils, wires, fluids, etc. either encapsulated, impregnated, wrapped around or otherwise attached to a vascular graft, patch, drape or other implantable medical device. The material of construction could be ePTFE, polyester, silicon, polyurethane or any other biomedical material. The design of the device and choice of the radioisotope material dictates the duration and strength of the radioactivity. The biomedical material envelopes and encapsulates the radioactive source preventing accidental release and providing a "spacer" between the source and the cellular tissue to be treated.

The present invention contemplates five primary embodiments, although one skilled in the art can appreciate a greater number of possibilities based on the inventive concepts herein. A first embodiment includes incorporating radioactive "seeds" (grains, granules, encapsulated radioactive fluid or other radioactive particles) into a graft either along its length or at proximal and distal ends. The seeds can be placed into the ePTFE or other biomedical material prior to extrusion (e.g., coextruded) or fabrication so that they will be embedded into the graft and will have an even distribution within the graft. A second embodiment uses radioactive seeds implanted in the biomedical material as in the first embodiment, but the end product is in the form of a "bandage" that is wrapped around a synthetic or natural vessel, irradiating the vessel to inhibit the tissue proliferation. A third embodiment incorporates radioactive wire into a graft by coiling the wire along its length or at isolated positions (e.g., near the point of anastamosis with the living vasculature). In the case of woven biomedical materials (e.g., polyester) the wire can be cowoven with the

biomedical material. The radioactive "wire" can actually be a beading of solid plastic (e.g., PTFE) which contains radioactive powder or seeds. Such beading can be readily laminated to biomedical graft material. A fourth embodiment includes impregnating radioactive agents into the wall of a graft. Finally, a fifth embodiment utilizes an encapsulated stent graft with pockets that are filled with radioactive material. This embodiment can be used intraluminally or as an interposition graft.

A more complete understanding of the radioactive grafts or cuffs will be afforded to those skilled in the art, as well as a realization of additional advantages and objects thereof, by a consideration of the following detailed description of the preferred embodiment. Reference will be made to the appended sheets of drawings which will first be described briefly.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a perspective view of a first embodiment of the present invention with radioactive seeds dispersed throughout a graft;

Fig. 2 is a cut-away view of a second embodiment of the present invention with the radioactive seeds of Fig. 1 dispersed throughout a cuff-like device;

Fig. 3 is a perspective view of a third embodiment of the present invention with a radioactive coil (wire or beading) wrapped around a graft;

Fig. 4 is a perspective view of a fourth embodiment of the present invention with pockets of radioactive fluid dispersed throughout a graft;

Fig. 5 is a diagrammatic cross-sectional view of a mandrel and die assembly which is used to extrude a graft (especially PTFE) containing radioactive agents.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

The present invention satisfies the need for a medical device to prevent restenosis through radioactive elements incorporated therein. This can be accomplished by mixing the radioactive seeds or powders into PTFE or other biomedical material before extrusion of the device so that the radioactive elements are evenly distributed throughout the resulting graft or cuff. Another method of incorporation is to wrap a solid radioactive element (wire or beading) around the device during manufacture or just prior to implanting into the body. It should be appreciated that the various devices can be fabricated with a non-radioactive component that is then rendered radioactive by neutron bombardment prior to use. This allows device manufacture without need to worry about radioactive contamination of the site or workers. Also, neutron bombardment can be used to generate radioactive isotopes with such short half-lives that normal manufacture and delivery would be impractical (that is, the radioactivity would be significantly decayed by the time the device was delivered).

Referring now to the drawings, in which like reference numbers represent similar or identical structures throughout, Fig. 1 illustrates a first embodiment of a radioactive graft **10**. The graft **10** is composed of a biomedical material (e.g., ePTFE) **14** with embedded radioactive seeds **12**. The seeds **12** (either solid particles or radioactive fluid droplets) are either co-extruded with the material already in a radioactive state, or are treated after

extrusion by neutron bombardment or the like. The latter method of forming the radioactive seeds 12 would present various advantages with respect to manufacturability, safety and shelf life. In the case where the material is PTFE or a similar substance extrusion will be explained with reference to Fig. 5 below.

By implanting the radioactive seeds 12 into the ePTFE covering 14, the use of the radioactive substance becomes wide ranging. The flexibility of the radioactive graft 10 enables it to be used in many applications such as on the inside or outside of a stent. With the radioactive element in the form of seeds, the radioactive properties can be manipulated based on need. Thus, if a longer duration of treatment is necessary, a long life, low energy isotope can be utilized; conversely, if a shorter more intense treatment is desired, a different isotope can be employed.

Fig. 2 illustrates a second embodiment of the present invention which is akin to the first embodiment. Radioactive cuff 20 includes a strip 24 made of any biomedical material, such as ePTFE that is nonabsorbable, with imbedded radioactive seeds 12. As shown in Fig. 2, the radioactive cuff 20 is wrapped around a body vessel 70 like a bandage, so that the radioactive seeds 12 irradiate the proliferating cells 72 within the vessel. This cuff 20 is extremely versatile and can be used in many different applications, including treatment of non-vascular malignancies such as those found in the synthetic replacement of a bile duct. In fact, radioactive cuff 20 can be utilized for nearly any tube or lumen in the body that is being occluded by a growth. As with the first embodiment, the radioactive properties of the seeds 12 can be chosen based on the specific application of the device, although an isotope with a

very long half life emitting relatively low energy radiation will normally be preferred. As in all cases of the present invention, the ePTFE prevents direct contact between the vascular tissue and the radioactive source. Thickness of the ePTFE can be selected to provide the ideal spacing between the source and the tissue.

Fig. 3 shows a third embodiment of the present invention. The graft structure 30 includes a graft or tubular member 34 with a radioactive wire 32 coiled radially around the outside surface, extending along its length. Beading as of PTFE containing radioactive material can be used in place of wire. Beading can be readily laminated to the graft as can wire clad in an appropriate plastic material. If the biomedical material is woven or knitted, the wire or beading can also be woven or knitted into the structure. The graft structure 30 can be used in conjunction with a stent in which the graft structure 30 is used to cover either a luminal or abluminal stent surface for insertion into a body lumen. The radioactive wire 32 would then act to reduce the possibility of restenosis after the stent was deployed by eliminating the proliferating cells. Most likely the radioactive wire or beading would be limited to the end regions of the graft 34 where it is sutured to the patient's vasculature. The radioactive wire 32 can be attached to the graft with adhesives. Alternatively, the wire can be coated with PTFE (e.g., by inserting the wire 32 into an elongate PTFE tube of a slightly greater diameter than the wire 32) or other plastic. This coated wire can then be adhered to the graft 34 through heat and pressure or through the use of an adhesive.

Fig. 4 illustrates a fourth embodiment of the present invention. In this embodiment, the radioactive agent is again incorporated into an ePTFE or other biomedical material

member. Here, the radioactive substance is in the form of a liquid wherein a radioactive solution is prepared and small droplets of the solution are encased by tiny plastic shells. The resulting radioactive balls 42 are co-extruded with the biomedical material, creating a radioactive graft 40 containing small pockets 46 filled with radioactive balls 42. Beside co-extruding techniques, the graft 40 can also be created by implanting or encapsulating the radioactive balls 42 after graft fabrication.

In a fifth embodiment, much like the first and third embodiments, radioactive or radiopharmaceutical agents are impregnated directly into the wall of an ePTFE graft without being aggregated as "seeds". In this case, the radioactive agent can come in the form of a ground up solid or powder which is coextruded with the PTFE. With reference to the first, third and fifth embodiments, Fig. 5 illustrates a ram extruder assembly 50 for co-extruding a billet of material, which in this case consists of PTFE mixed with any of the radioactive agents described. The ram extruder assembly 50 includes an extrusion barrel 52, an extrusion die 54, a mandrel 56, and a ram 58. The billet of material 59 is placed within the extrusion barrel 52. Force is applied to ram 58 which in turn expels pressure on the billet of material 59. The pressure causes the billet of material 59 to be extruded around the mandrel 56, through the extrusion die 54 so that it issues as a tubular extrudate 60. An arrow 82 shows the direction of the extrusion. The tubular extrudate 60 is then expanded and sintered in accordance with the expansion and sintering procedures undertaken with pure PTFE vascular grafts which are well known in the art. Where plastic encased radioactive liquid ball 42 are used, encapsulation materials are selected so that the extrusion process does not

result in rupture of the balls 42 and release of radioactive liquid.

Having thus described a preferred embodiment of the radioactive graft, it will be apparent to those skilled in the art how certain advantages of the present invention have been achieved. It should also be appreciated that various modifications, adaptations, and alternative embodiments thereof may be made within the scope and spirit of the present invention. Some examples have been illustrated with ePTFE as a biomedical material, but it should be apparent that the inventive concepts described above would be equally applicable to polyester, organosilicon, polyurethane or any other biomedical material that can be extruded or woven. Moreover, the words used in this specification to describe the invention and its various embodiments are to be understood not only in the sense of their commonly defined meanings, but to include by special definition in this specification. Thus, if an element can be understood in the context of this specification as including more than one meaning, then its use in a claim must be understood as being generic to all possible meanings supported by the specification and by the word itself. The definitions of the words or elements of the following claims are, therefore, defined in this specification to include not only the combination of elements which are literally set forth, but all equivalent structure, material or acts for performing substantially the same function in substantially the same way to obtain substantially the same result. The described embodiments are to be considered illustrative rather than restrictive. The invention is further defined by the following claims.

CLAIMS

We Claim:

1. An implantable radioactive device for preventing tissue proliferation, comprising:

an underlying structure composed of pliable material; and

a radioactive element incorporated into said underlying structure.

2. The implantable radioactive device of Claim 1, wherein said underlying structure is a vascular graft for replacement of a body vessel.

3. The implantable radioactive device of Claim 1, wherein said underlying structure is a cuff for placement over a body vessel.

4. The implantable radioactive device of Claim 3, wherein said radioactive element comprises a plurality of radioactive seeds.

5. The implantable radioactive device of Claim 4, wherein said radioactive seeds are mixed into and co-extruded with the underlying structure.

6. The implantable radioactive device of Claim 2, wherein said radioactive element comprises a plurality of radioactive seeds.

7. The implantable radioactive device of Claim 6, wherein said radioactive seeds are mixed into and co-extruded with the underlying structure.

8. The implantable radioactive device of Claim 1, wherein said radioactive element comprises a flexible wire.

9. The implantable radioactive device of Claim 8, wherein said wire is coiled around the exterior of said vascular graft.

10. The implantable radioactive device of Claim 8, wherein said wire is coiled around the interior of said vascular graft.

11. The implantable radioactive device of Claim 1, wherein said radioactive element comprises beading.

12. The implantable radioactive device of Claim 11, wherein said wire is coiled around the exterior of said vascular graft.

13. The implantable radioactive device of Claim 11, wherein said wire is coiled around the interior of said vascular graft.

14. The implantable radioactive device of Claim 1, wherein said radioactive element comprises particles of encapsulated radioactive liquid.

15. The implantable radioactive device of Claim 1, wherein said radioactive element comprises small solid particles.

16. The implantable radioactive device of Claim 1, wherein said underlying structure is composed of a material selected from the group consisting of expanded polytetrafluoroethylene, polyester, silicone rubber, polyurethane, and fluoropolymers.

17. An implantable radioactive device for preventing tissue proliferation, comprising:

an extruded member of expanded polytetrafluoroethylene; and

a plurality of radioactive sources incorporated into and co-extruded with said extruded member.

18. An implantable radioactive device for preventing tissue proliferation, comprising:

an extruded tubular member of expanded polytetrafluoroethylene; and

a radioactive wire wrapped around said tubular member.

19. The implantable radioactive device of Claim 18, wherein said radioactive wire is coated with an organic plastic material.

20. The implantable radioactive device of Claim 19, wherein said plastic material is polytetrafluoroethylene.

21. A process for producing an implantable radioactive device for preventing tissue proliferation comprising the steps of:

selecting a particle consisting of a material that can be rendered radioactive;

making a mixture of a plurality of the non-radioactive particles with a plurality of polytetrafluoroethylene particles with a liquid;

forming an extrudate by extruding the mixture;

expanding the extrudate; and

treating the extrudate to render said non-radioactive particles radioactive.

AMENDED CLAIMS

[received by the International Bureau on 23 January 2001 (23.01.01); original claims 1-21 replaced by new claims 1-10 (2 pages)]

1. An implantable radioactive device for preventing tissue proliferation, comprising an underlying structure composed of pliable material, wherein a radioactive element is incorporated therein, ***characterized in that*** the radioactive element is selected from the group consisting of radioactive powder, radioactive solid particles (12) and units of encapsulated radioactive liquid (42).

2. The implantable radioactive device according to claim 1, wherein the underlying structure is selected from the group consisting of a graft (10) and a cuff (20).

3. The implantable radioactive device as in claims 1 or 2, wherein the pliable material is selected from the group consisting of expanded polytetrafluoroethylene, polyester, silicone rubber, polyurethane, and fluoropolymers.

4. An implantable radioactive device for preventing tissue proliferation, comprising a graft (34) composed of pliable material, having a radioactive component associated therewith, ***characterized in that*** the radioactive component comprises a coiled flexible wire (32) extending at least partially along the longitudinal axis of the graft.

5. The implantable radioactive device according to claim 4, wherein the flexible wire further comprises a beading of solid plastic, having a radioactive element contained therein.

6. The implantable radioactive device as in claims 4 or 5, wherein the flexible wire is adhered to the exterior of the graft.

7. The implantable radioactive device as in claims 4 or 5, wherein the flexible wire is woven into the graft.

8. The implantable radioactive device as in any of claims 4, 6 or 7, wherein the flexible wire is coated with an organic plastic material.

9. The implantable radioactive device as in any of claims 4-8, wherein the graft is composed of a material selected from the group consisting of expanded polytetrafluoroethylene, polyester, silicone rubber, polyurethane, and fluoropolymers.

10 A process for producing an implantable radioactive device for preventing tissue proliferation, comprising the step of selecting a plurality of particles (12, 42) comprising a material that can be rendered radioactive, ***characterized by*** combining the particles (12, 42) with a plurality of polytetrafluoroethylene particles and a liquid, forming an extrudate by extruding the mixture, expanding the extrudate; and treating the extrudate to render the particles radioactive.

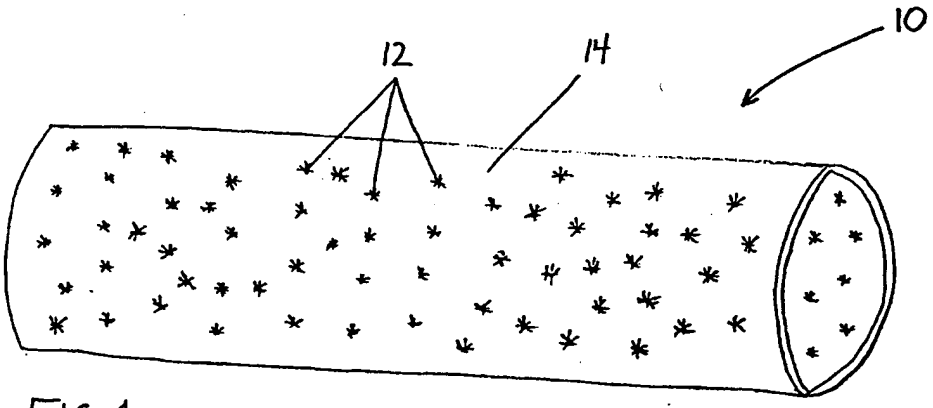

FIG 1

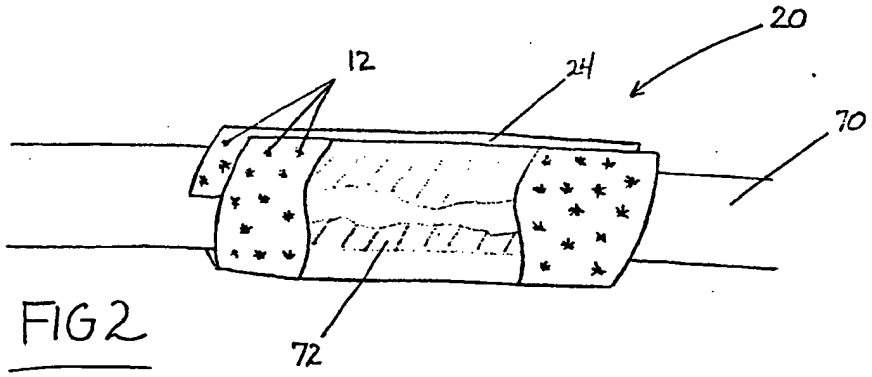

FIG 2

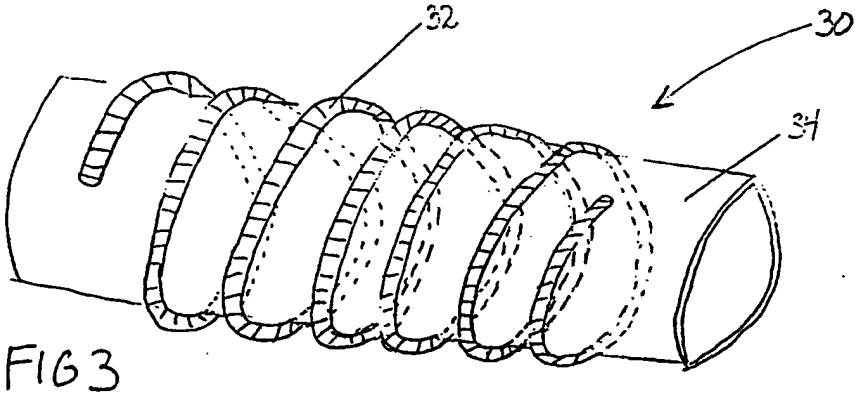

FIG 3

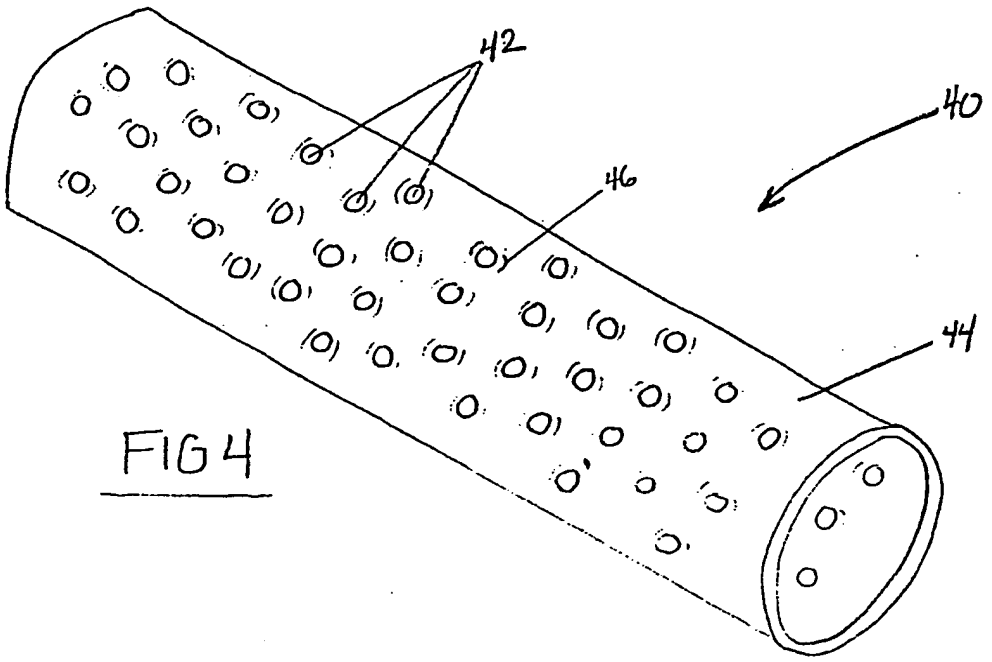

FIG 4

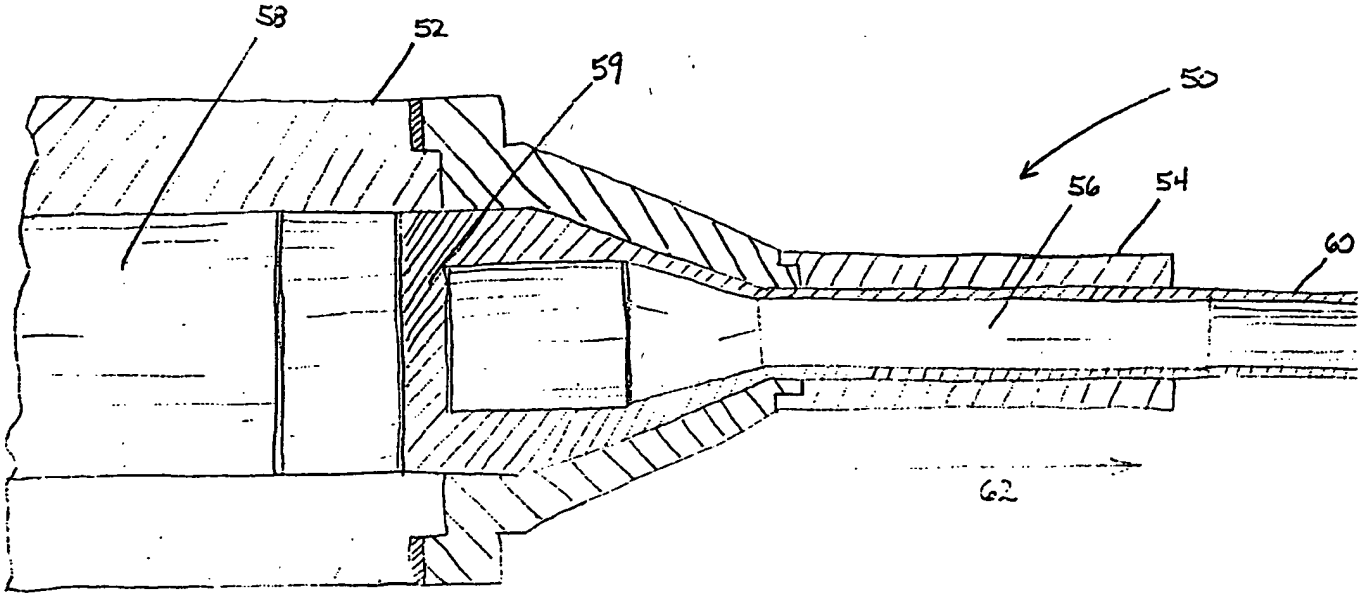

FIG 5

Prior Art

INTERNATIONAL SEARCH REPORT

Inte. nal Application No
PCT/US 00/26111

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61F2/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	WO 99 37243 A (RIGITEC B.V.) 29 July 1999 (1999-07-29) the whole document	1-13,15, 17,18 21
X	US 5 873 811 A (WANG ET AL) 23 February 1999 (1999-02-23) the whole document	1,2,6,7, 15-17
A	EP 0 857 470 A (SORIN BIOMEDICA CARDIO S.P.A.) 12 August 1998 (1998-08-12)	

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search	Date of mailing of the international search report
27 November 2000	04/12/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Smith, C

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte. nal Application No
PCT/US 00/26111

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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